

The Journal of the Association for Vascular Access

Comparison of the Safety and Efficacy of Two Topical Antiseptic Products: Chlorhexidine Gluconate + Isopropyl Alcohol and Povidone-Iodine + Isopropyl Alcohol

Greg Art, BA, MBA

Abstract

While antiseptic products containing a combination of chlorhexidine gluconate and isopropyl alcohol (CHG+IPA) have gained in popularity over the past several years in preparing and maintaining vascular access sites, the data used to support their use over products containing povidone-iodine (PVP-I) have been based solely on comparisons of aqueous CHG or CHG+IPA to aqueous PVP-I alone. No studies have compared aqueous CHG or CHG+IPA to PVP-I+IPA or aqueous PVP-I preceded by IPA. When compared using methods established by the U.S. Food and Drug Administration (FDA) and the American Society of Testing and Materials (ASTM), the safety and efficacy of PVP-I+IPA was found to be less irritating and faster acting than CHG+IPA; both PVP-I+IPA and CHG+IPA demonstrated persistence for 7 days.

In the United States, aqueous povidone-iodine (PVP-I) has, for many years, been the most widely used antiseptic for cleansing arterial catheter and central venous catheter insertion sites.¹ Based on a pivotal study by Maki et al² demonstrating chlorhexidine gluconate (CHG) to be more effective than PVP-I in reducing catheter-related infections, the U.S. Centers for Disease Control (CDC) published its 2002 *Guidelines for the Prevention of Intravascular Catheter-Related Infections* which, in part, stated that “a 2% chlorhexidine-based preparation is preferred.”³ That same year (2002), the first formulation containing a combination of CHG and an antiseptically effective concentration of isopropyl alcohol (IPA; 70%) was introduced in the United States (Chloraprep®, 2% CHG+70% IPA; Enturia, Inc., Leawood, KS).

Since that time, a significant number of studies have been published reporting superior efficacy and/or cost savings with CHG versus PVP-I formulations.^{4,5,6,7,8,9} As a result, many professional standards and guidances now recommend the use of CHG over PVP-I.^{3,10,11,12,13,14}

However, it is important to note that the studies referenced above compared a *combination* CHG+IPA formulation with formulations containing PVP-I alone. Given the widely recognized, substantial effectiveness of alcohol, including the CDC considering it “the most effective and rapid-acting skin antiseptic,”¹⁵ and its undoubted contribution to the effectiveness of formulations in which it is included, the prevailing conclusion from these studies that formulations containing CHG are superior to those containing PVP-I, whether alcohol is present or not, is erroneous.

Maki et al² demonstrated that *aqueous* 2% CHG is more effective than *aqueous* PVP-I in reducing catheter-related infections, and the studies referenced above demonstrate that 2% CHG combined with 70% IPA is more effective than *aqueous* PVP-I. However, while formulations containing a combination of PVP-I and alcohol have been available for some time with documented enhanced efficacy over formulations containing either PVP-I or alcohol alone,¹⁶ to the author’s knowledge, this article is the first to report results from studies directly comparing products containing a combination of PVP-I and alcohol (ExCel_{AP}®, 7.5% PVP-I, 72% IPA; Aplicare, Inc., Meriden, CT) with products containing a combination of CHG and alcohol (Chloraprep®, 2% CHG+70% IPA, Enturia, Inc.; Leawood, KS).

Correspondence concerning this article should be addressed to gregart@aplicare.com
DOI: 10.2309/java.12-3-12

Regulatory Considerations

From a clinical perspective, antiseptic formulations can be used for a variety of purposes including health-care personnel hand washing, surgical hand scrubbing, patient preoperative skin prepping, and catheter site maintenance. However, it is important for clinicians to understand that not all antiseptic products are approved or should be used for all of the above indications.

Indications and Active Ingredients

The U.S. Food and Drug Administration's (FDA) Tentative Final Monograph (TFM) entitled "Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products"¹⁷, defines a *patient preoperative skin preparation* as "a fast-acting [rapidly kills microorganisms] broad-spectrum [kills a wide spectrum of microbial species] persistent [suppresses regrowth of remaining micro-organisms] antiseptic-containing preparation that significantly reduces the number of micro-organisms on intact skin."¹⁷ In this TFM, the FDA lists those active ingredients which it classifies as "generally recognized as safe and effective"¹⁷ (Category I) for preparation of the skin prior to surgery. They are:

- Ethyl alcohol or ethanol (EtOH) 60% to 95%;
- Isopropyl alcohol or 2-propanol (IPA) 70% to 91%;
- Iodine topical solution U.S.P. (aqueous); contains between 1.8 and 2.2 g iodine (I₂) and between 2.1 and 2.6 g sodium iodine (NaI) in each 100 mL of solution;¹⁸
- Iodine tincture U.S.P.; essentially Iodine Topical Solution, USP, where half of the water has been replaced with ethyl alcohol;¹⁸ and
- PVP-I 5% to 10%; a solution of PVP-I containing between 85% and 120% of the labeled amount of iodine (I₂).¹⁹

For formulations *specifically* containing PVP-I, the FDA recognizes patient preoperative skin preparations as a broad category which includes preparation of the skin prior to surgery and other applications such as skin prepping prior to injection, catheter site care, and intravenous site preparation.¹⁷ With the exception of formulations containing between 60% and 95% EtOH or 70% to 91% IPA which can be indicated for use "for preparation of the skin prior to an injection,"¹⁷ the TFM does not address other active ingredients (eg, tincture of iodine, CHG) for these additional indications.

Because the TFM recognizes Category I ingredients including PVP-I ranging in concentrations between 5% and 10%, and IPA in concentrations between 70% and 91% as generally safe and effective for preparation of the skin prior to surgery, no agency approval is required prior to marketing.

Formulations indicated for preparation of the skin prior to surgery containing active ingredients other than those listed above as Category I (ie, those that are not recognized as generally safe and effective and specifically excluded and therefore not applicable to the TFM; eg, CHG) can only be marketed in the United States after receiving approval from the FDA for specific indications through the New Drug Application or Abbreviated New Drug Application (NDA, ANDA) process.

Testing

All testing reported herein was conducted at Bioscience Laboratories (Bozeman, MT). This is one of the top three independent testing organizations recognized by the FDA as qualified to carry out the studies described.

Safety Testing

Background

Regardless of how effective an antiseptic formulation might be, it is important that the formulation be safe for the duration of its intended use. For topical antiseptics, skin irritation potential is a key safety parameter to be evaluated.

Antiseptic products intended for repeated applications (eg, catheter site maintenance where the product may be applied weekly for many months), are required by the FDA to either pass a 21-day cumulative irritation study consistent with the protocol described below or submit results obtained during actual-use clinical trials demonstrating the product is sufficiently nonirritating to be used repeatedly.

Twenty-One Day Cumulative Skin Irritation

Purpose

The purpose of this test was to determine whether the skin irritation potential of a combination PVP-I+IPA formulation (ExCel_{AP}; Aplicare, Inc., Meriden, CT) is suitably nonirritating to allow for repeated use.

Methodology

Consistent with FDA's guidance for skin irritation and sensitization testing of generic transdermal drug product,²⁰ approximately 0.02 mL of the combination PVP-I+IPA formulation was applied to contralateral paraspinal regions of the upper back of 30 human subjects. Before occlusion with a Finn Chamber,²¹ the formulation was applied wet to one site and allowed to completely air dry on a second site. A positive control (0.1% sodium lauryl sulfate solution) was applied wet to a third site.

All test sites were occluded with a Finn Chamber for 23 ± 1 hours. Following exposure, sites were scored for irritation using a standardized scale:²⁰

- 0 = *no evidence of irritation*;
- 1 = *minimal erythema, barely perceptible*;
- 2 = *definite erythema, readily visible; minimal edema or minimal papular responses*;
- 3 = *erythema and papules*;
- 4 = *definite edema, etc.*

The procedure was then repeated on the same test sites an additional 20 times (over 20 days). Site treatment was discontinued when a score of greater than 3 was reached.

Pass/Fail Criteria

A test product is considered to have passed if fewer subjects are discontinued by virtue of having an irritation score of greater than 3 when treated with the test product than those discontinued when treated with the positive control (ie, the test product must be no more irritating than the positive control).

Results

The percentage of subjects discontinued after exposure to the combination PVP-I+IPA formulation when applied and allowed to dry was 76.6%; when applied and occluded wet, it was 80%. 96.7% of subjects exposed to the control product were discontinued.

Discussion

The combination PVP-I+IPA formulation, when applied either wet or allowed to dry, was nominally less irritating than the positive control and is therefore considered by FDA standards to have a skin irritation potential within acceptable limits for a repeated use product.

Although no CHG+IPA combination formulation was included in this study, excerpts from FDA's "Medical Review" of Enturia, Inc.'s New Drug Application for ChloraPrep (NDA# 20-832)²² strongly suggest that the product did not pass an evaluation of its potential to cause irritation similar to the one described here. On page two under item three of this document, the reviewer states, "The combination product appears to be too irritating to be used under occlusive dressings. In any resubmission of this application, information/data must be presented which establish the safety of such use, given that the irritancy and sensitisation testing suggest that the product would be unacceptable to the patient when used under occlusion."²² On page 14 of the document, the FDA reviewer states, "ChloraPrep demonstrated a relatively high potential to cause irritation and sensitization reactions in predictive skin testing. It scored much higher in irritancy testing than Hibiclens [remaining text redacted by FDA]. Concern was also voiced that repeated use could exacerbate the irritation/sensitization possibilities."²² Finally, at the top of page 15, the reviewer states, "These concerns have been satisfied by the decision to indicate the product for use as a patient preoperative skin preparation. This is a one time use [remaining text redacted by FDA]. Thus, while the product is irritating, its intended indication does not prohibit its use. The margin of safety available to the patient under these [one time use] conditions is acceptable."²²

Data from the ChloraPrep Clinical Compendium²³ published by the manufacturer provides no information to the contrary. In the study reported, the products tested were only applied to the skin three times over a five-day period versus 21 times over a 21-day period. More important, the final formulation containing *both* 2% CHG and 70% IPA was not tested. Conclusions about the irritation potential of a formulation cannot be drawn from tests of its individual ingredients—the final formulation itself must be tested.

Discussion and Conclusions

These results demonstrate the suitability of the 7.5% PVP-I+72% IPA formulation for repeated topical antiseptic use; no published data could be found to support repeated use for the 2% CHG+70% IPA formulation.

Efficacy Testing

Study 1

Study 1 compared a product containing a combination of

7.5% PVP-I+72% IPA with a product containing the combination 2% CHG+70% IPA as patient preoperative and precatheter/catheter site maintenance skin preparations.

Purpose

The purpose of this study was to evaluate the relative performance and suitability as a patient preoperative and precatheter/catheter site maintenance preparation a product containing a combination 7.5% PVP-I+72% IPA formulation (ExCel_{AP} triple swabsticks; Apicare, Inc., Meriden, CT) and a product containing a combination 2% CHG+70% IPA formulation (ChloraPrep 3 mL; Enturia, Inc., Leawood, KS) when applied per their labeled application directions.

Methods

In accordance with FDA's "Good Clinical Practices"²⁴ and consistent with protocols described in the TFM and/or by the American Society for Testing and Materials' *Standard Test Method for Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations* (ASTM E 1173-01),²⁵ after Institutional Review Board approval, healthy human subjects between the ages of 18 and 70 were recruited and, for a 14-day pre-test period, provided a personal hygiene kit for exclusive use during the course of the study. In addition, subjects were instructed to avoid the use of medicated soaps, lotions, shampoos, deodorants, and so forth, as well as skin contact with solvents, acids, and bases. Subjects were also instructed to avoid using ultraviolet tanning beds or bathing in antimicrobial-treated (eg, chlorinated) pools and/or hot tubs. Finally, subjects did not shave the anatomical sites to be tested during the five days prior to being treated with the test products and did not bathe or shower within the 48 hour period prior. This regimen allowed for the stabilization of the normal microbial flora of the skin. During the latter portion of the week of the pretest period (at least 48 hours prior to the test day the following week), hair on the sampling sites was clipped.

Two anatomical sites were used: the inguinal area (groin; 8-9 subjects) and the abdomen (7-10 subjects). For the patient preoperative skin preparation evaluation, inguinal site sampling was performed immediately (within 30 seconds of drying), and at approximately 6 and 24 hours post-product application. For the patient precatheter/catheter site maintenance skin preparation evaluation, abdominal sites were sampled 24 hours, 48 hours, and 7 days post-product application.

Test products were randomly assigned to subjects, such that one test product was applied to one side, and another one to the other side of each subject. Just prior to product application, microbial samples were taken at each of the various anatomical sites using the Cylinder Sampling Technique.²⁶ This technique involves removing microorganisms from the skin using a small, flexible, rubber spatula and liquid recovery medium. From these samples, the baseline count of microorganisms on the skin was determined. Prepping was then performed with the assigned products and application directions and the sites were then sampled again at the various post-prep time points.

Application instructions for the combination 7.5% PVP-I+72% IPA product on inguinal sites was to use a back and forth prepping procedure for 40 seconds with the first two swabsticks

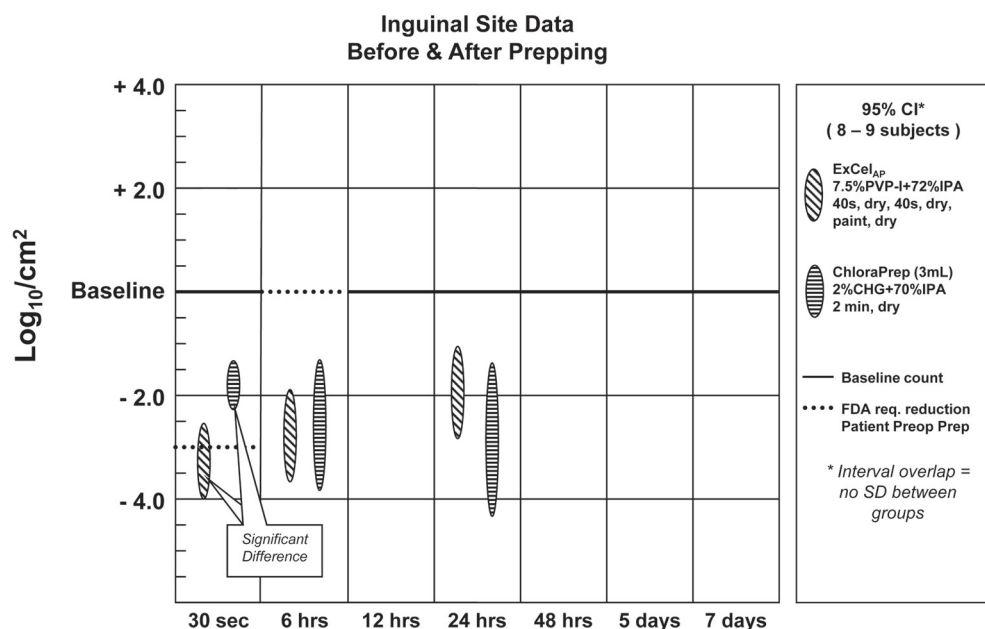


Figure 1. Comparison of products containing a combination 7.5% PVP-I+72% IPA to a combination 2% CHG+70% IPA as “moist site”¹⁷ patient pre-operative, precatheter/catheter site maintenance skin preparations. CI = confidence interval; req. = required. See text for product information.

(allowing the prepped area to dry after the use of each swabstick) and then painting the prepped area using the third swabstick and allowing to dry. The combination 2% CHG+70% IPA product was used per the product’s application instructions (ie, “Use repeated back and forth strokes of the sponge for approximately 2 minutes. Completely wet the treatment area with antiseptic. Allow the area to dry for approximately 30 seconds. Do not blot or wipe away”²⁷).

Application instructions for the combination 7.5% PVP-I+72% IPA product on abdominal sites was to use a back and forth prepping procedure for 30 seconds with the first two swabsticks (allowing the prepped area to dry after the use of each swabstick) and then painting the prepped area using the third swabstick and allowing to dry. The combination 2% CHG+70% IPA product was used per the product’s application instructions (ie, “Use repeated back and forth strokes of the sponge for approximately 30 seconds. Completely wet the treatment area with antiseptic. Allow the area to dry for approximately 30 seconds. Do not blot or wipe away”²⁷).

Pass/Fail Criteria

According to the TFM, an antiseptic product is considered to be an effective patient preoperative skin preparation for “moist”¹⁷ surgical sites (eg, groin) if, when used according to the labeled directions, it achieves a 3 $\text{log}_{10}/\text{cm}^2$ reduction in microorganism populations within 10 minutes post-product application and maintain those populations below baseline for at least six hours.¹⁷ For “dry”¹⁷ surgical sites (eg, abdomen, subclavian), it must achieve a 2 $\text{log}_{10}/\text{cm}^2$ reduction in microorganism populations within 10 minutes post-product application and maintain those populations below the original, pre-treatment baseline for at least six hours.¹⁷

While preparation of the skin prior to insertion of a catheter is considered a patient preoperative skin preparation, catheter site maintenance is not addressed in the TFM as a separate indication with specific performance criteria, and the ASTM standard test method²⁵ (not recognized by the FDA) does not specify effi-

cacy standards for this use.

Results

The product containing a combination 7.5% PVP-I+72% IPA formulation applied as described above met the TFM requirements as a moist site patient preoperative skin preparation (3 $\text{log}_{10}/\text{cm}^2$ reduction within 10 minutes, not to exceed baseline before six hours). It achieved an average initial $\text{log}_{10}/\text{cm}^2$ reduction of 3.23 and an average $\text{log}_{10}/\text{cm}^2$ reduction of 2.80 six hours after application. The product containing a combination 2% CHG+70% IPA product failed to achieve the required initial 3 $\text{log}_{10}/\text{cm}^2$ reduction to be considered an effective moist site patient preoperative skin preparation. It achieved an average initial $\text{log}_{10}/\text{cm}^2$ reduction of 1.80 and an average $\text{log}_{10}/\text{cm}^2$ reduction of 2.57 six hours after application.

When applied to inguinal sites per the directions described above, the product containing a combination 7.5% PVP-I+72% IPA formulation demonstrated significantly ($p<0.05$) greater efficacy than the product containing a combination 2% CHG+70% IPA formulation 30 seconds post-product application and nominally, but not significantly ($p\geq 0.05$) greater at six hours post-product application. $\text{Log}_{10}/\text{cm}^2$ reductions achieved by the product containing a combination 2% CHG+70% IPA formulation were nominally, but not significantly ($p\geq 0.05$) greater than the product containing a combination 7.5% PVP-I+72% IPA at 24 hours post-product application (see Figure 1).

When applied to abdominal sites per the directions described above, the product containing a combination 7.5% PVP-I+72% IPA formulation demonstrated nominally, though not significantly ($p\geq 0.05$) less efficacy than the product containing a combination 2% CHG+70% IPA formulation at the 24 hour (mean $\text{log}_{10}/\text{cm}^2$ reduction of 1.84 PVP-I+IPA vs. 2.42 CHG+IPA), 48 hour (mean $\text{log}_{10}/\text{cm}^2$ reduction of 2.02 PVP-I+IPA vs. 2.43 CHG+IPA), and seven day (mean $\text{log}_{10}/\text{cm}^2$ reduction of 1.11 PVP-I+IPA vs. 1.86 CHG+IPA) post-application time points. Both the product containing a combination 7.5% PVP-I+72% IPA formula-

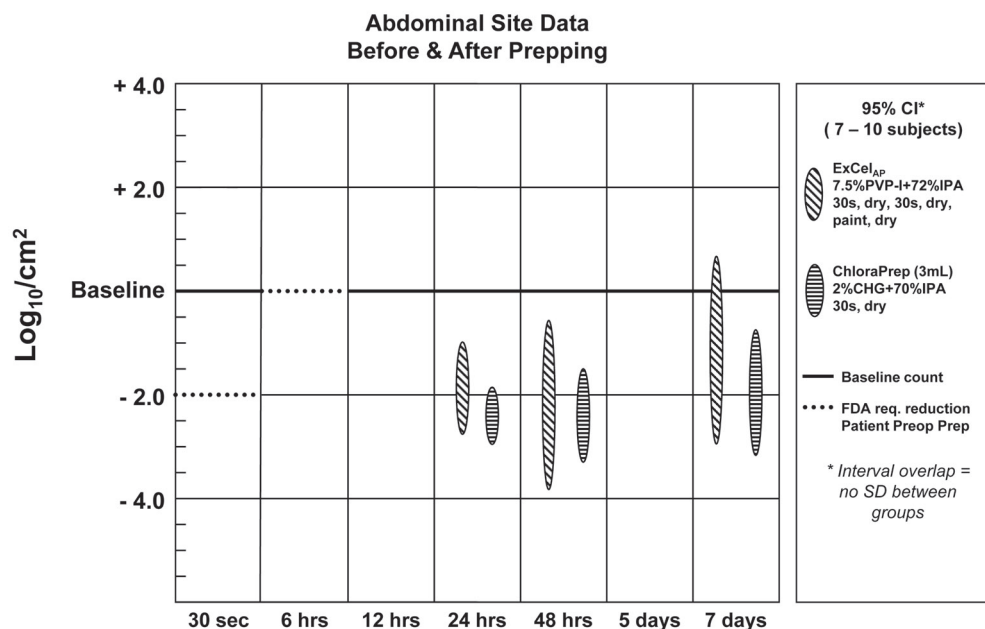


Figure 2. Comparison of products containing a combination 7.5% PVP-I+72% IPA to a combination 2% CHG+70% IPA as dry-site catheter site maintenance skin preparations. CI = confidence interval; req. = required. See text for product information.

tion and the product containing a combination 2% CHG+70% IPA formulation maintained microorganism populations below baseline for the entire seven day duration of the study (see Figure 2).

Discussion and Conclusions

Microbial $\text{log}_{10}/\text{cm}^2$ reductions achieved by the products containing either a combination 7.5% PVP-I+72% IPA formulation or a combination 2% CHG+70% IPA formulation as applied indicate their suitability as a patient preoperative skin preparation product. While no performance criteria are specified by either the TFM or ASTM for products used for central venous catheter site maintenance, both products tested maintained microbial counts below baseline for seven days.

With one exception, no significant difference ($p \geq 0.05$) was determined between the efficacy of the product containing a combination 7.5% PVP-I+72% IPA formulation and the product containing a combination 2% CHG+70% IPA formulation; the products performed equally. However, a significantly ($p < 0.05$) greater $\text{log}_{10}/\text{cm}^2$ reduction was achieved by the product containing a combination 7.5% PVP-I+72% IPA formulation on inguinal sites immediately after product application, suggesting the product containing a combination 7.5% PVP-I+72% IPA as being superior to the product containing a combination 2% CHG+70% IPA as a fast-acting antiseptic.

Study 2

Study 2 compared the antimicrobial efficacy of a product containing a combination 7.5% PVP-I+72% IPA formulation with a product containing a combination 2% CHG+70% IPA formulation as a patient preinjection skin preparation.

Purpose

To evaluate the relative performance and suitability as a patient preinjection skin preparation, a product containing a combination 7.5% PVP-I+72% IPA formulation (ExCel_{AP} single

swabsticks; Apicare, Inc., Meriden, CT) and a product containing a combination 2% CHG+70% IPA formulation (ChloraPrep Sepp®, 0.67 mL; Enturia, Inc., Leawood, KS) when applied per their labeled application directions.

Methods

The methods used in this study were the same as Study 1 above, with the following exceptions:

1. Only the median cubital region of the arm was tested; 11-12 subjects were tested with each product.
2. Sampling was only performed immediately (within 30 seconds of drying) after product application.
3. Application instructions for the product containing a combination 7.5% PVP-I+72% IPA formulation was to use one swabstick in a back and forth prepping procedure for 10 seconds and allow to dry. The product containing a combination 2% CHG+70% IPA was used per the product's application instructions (ie, "Use repeated back and forth strokes of the sponge for approximately 30 seconds. Completely wet the treatment area with antiseptic. Allow the area to dry for approximately 30 seconds. Do not blot or wipe away").²⁸

Pass/Fail Criteria

According to the TFM, an antiseptic product is considered to be an effective patient preinjection skin preparation if, when used according to the labeled directions, it achieves a 1 $\text{log}_{10}/\text{cm}^2$ decrease in microorganism populations within 30 seconds post-product application.¹⁷

Results

Both the product containing a combination 7.5% PVP-I+72% IPA formulation and the product containing a combination 2% CHG+70% IPA formulation, applied as described above, met the TFM requirements to validate their use as a patient preinjection skin preparation.

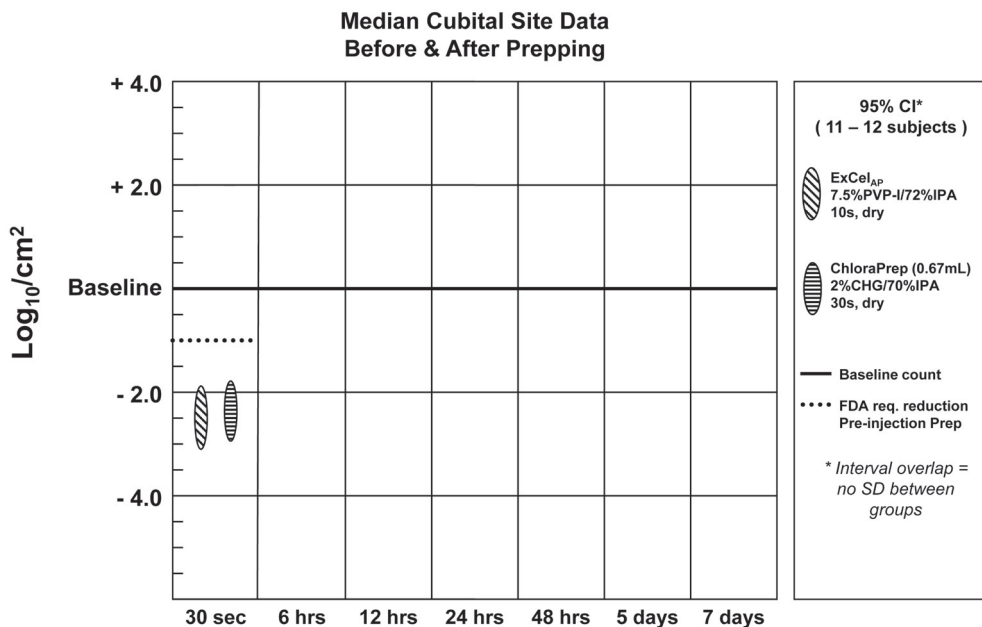


Figure 3. Comparison of a product containing a combination 7.5% PVP-I+72% IPA formulation with a product containing a combination 2% CHG+70% IPA formulation as a preinjection site skin preparation. CI = confidence interval, req. = required. See text for product information.

$\text{Log}_{10}/\text{cm}^2$ reductions achieved by the product containing a combination 7.5% PVP-I+72% IPA formulation applied to the skin for 10 seconds was nominally (mean $\text{log}_{10}/\text{cm}^2$ reduction of 2.53), but not significantly ($p \geq 0.05$), greater than the product containing a combination 2% CHG+70% IPA formulation when applied to the skin for 30 seconds (mean $\text{log}_{10}/\text{cm}^2$ reduction of 2.37) (see Figure 3).

Discussion and Conclusions

When used according to the manufacturers' directions, both the product containing a combination 7.5% PVP-I+72% IPA formulation and the product containing a combination 2% CHG+70% IPA formulation can be considered effective patient preinjection skin preparations. However, the product containing a combination 7.5% PVP-I+72% IPA formulation met this requirement using one third the application time (10 vs. 30 seconds). No significant difference ($p \geq 0.05$) was determined between the efficacy of the product containing a combination 7.5% PVP-I+72% IPA formulation applied to the skin for 10 seconds and the product containing a combination 2% CHG+70% IPA formulation applied for 30 seconds; the products performed equally.

Overall Discussions and Conclusions

While making generalities about the *relative* effectiveness of different antiseptic ingredients is tempting (eg, CHG is more effective than PVP-I), it is important to understand that antiseptic ingredients are not delivered to the skin by themselves; they're delivered in *products* consisting of specific volumes of distinct formulations with specific application directions. Thus, the actual safety and effectiveness of any particular antiseptic *product* is dependent on a wide variety of factors including:

1. The concentration of the active ingredient(s). In most cases, the higher the concentration of active ingredients, the greater the efficacy, but generally also the greater the cost and irritation potential.

2. The presence or absence of either EtOH (60%-95%) or IPA (70%-91%). As mentioned in the introductory section of this article, in the CDC's most recent guidance for the prevention of surgical site infection, states that alcohol is "the most effective and rapid-acting skin antiseptic."¹⁵ Indeed, studies submitted to the FDA as part of Enturia, Inc.'s New Drug Application for ChloraPrep (NDA# 20-832) showed no difference in either the immediate (one minute post-product application) or persistent (6 and 24 hours post-product application) efficacy between ChloraPrep 2% CHG+70% IPA and 70% IPA alone.²⁹ Alcohol offers the additional benefit of reducing procedure time by causing formulations that contain it to dry more rapidly. Recognizing the benefits of including alcohol in combination with CHG and PVP-I formulations, the 2006 Infusion Nursing Society's *Standards of Practice* state "Formulations containing a combination of alcohol (ethyl or isopropyl) and either chlorhexidine gluconate or povidone-iodine are preferred" for access site preparation (Standard 41) and catheter site care (Standard 51).³⁰
3. The presence or absence of various inactive ingredients (eg, buffering and film-forming agents, surfactants, emollients, colorants, fragrances) included in the formulation. Many surfactants and emollients deactivate certain antiseptic agents. For example, CHG is deactivated by anionic surfactants and must be formulated only with cationic or ionically neutral ingredients.³¹ A CHG formulation containing anionic ingredients would essentially be no more effective than plain soap. pH can also have a substantial influence on the efficacy of an antiseptic formulation. The presence or absence of film-forming agents which can cause antiseptic ingredients to remain in contact with the skin for longer periods of time can influence a product's persistence. Thickening agents can lead to less of the formulation running off the treatment area before killing any microorganisms. In other words, not all formulations containing the same active ingredient(s), even at the same concen-

- trations, can necessarily be expected to perform the same.
4. The time the antiseptic formulation is in contact with the skin (ie, the application time). In most cases, the longer the antiseptic is in contact with the area being treated, the more bacteria are killed. This, of course, typically comes at a cost in terms of procedure time and greater irritation potential.
 5. The volume of solution applied relative to the area of skin being treated. One would not expect to be able to prep an entire leg with 1 mL of any antiseptic formulation.
 6. The manner in which the formulation is applied (eg, firm scrubbing vs. gentle painting; back and forth motion vs. circular motion). More aggressive scrubbing allows for greater penetration of the antiseptic into deeper layers of the skin where some microorganisms exist. However, excessive scrubbing can also lead to the skin being damaged; resulting in the creation of an environment favorable to the regrowth of microorganisms.
 7. The shape and abrasiveness of the delivery system (typically gauze or foam-tipped applicator) used to apply the formulation to the skin. Some applicators make it easier than others to apply antiseptics to skin surfaces with varying contours such as fingers and toes. The abrasiveness of foam applicators can affect the extent to which an antiseptic penetrates into deeper layers of the skin with the same level of force applied.
 8. The presence or absence of additional active ingredients and the possible synergistic or deleterious effects between actives having different modes of action. For example, the study by Maki et al² (which led to the CDC's recommendation that "a 2% chlorhexidine-based preparation is preferred" for catheter site care) evaluated a 2% aqueous (nonalcoholic) CHG solution, which is inherently less irritating than what the FDA found a product containing a combination 2% CHG+70% IPA to be for repeated use.²²

As such, it is important for clinicians to understand that studies do not compare active ingredients. Rather, they compare products which contain specific volumes of both active and inactive ingredients in specific concentrations applied with specific applicators using specific directions for use. By manipulating the above parameters, it is relatively easy to demonstrate that any particular antiseptic active ingredient is superior to another. Clinicians need to be mindful of these efficacy-influencing factors and be careful with respect to the conclusions they draw from published studies. One, or even many studies showing that a formulation containing active ingredient "A" is superior to formulations containing active ingredient "B" do not necessarily translate to the conclusion that all formulations containing active ingredient "A" are superior to those containing active ingredient "B."

The studies reported herein demonstrate that while products containing formulations of CHG alone are *generally* more effective than products containing formulations of PVP-I alone, and combination formulations containing CHG and IPA are more effective than PVP-I alone, the particular product tested containing a combination formulation of 7.5% PVP-I and 72% IPA, and when used as described is equally broad spectrum, equally persistent, but faster acting and less irritating than products containing a combination formulation of 2% CHG and 70% IPA.

When selecting an antiseptic regime, clinicians should cer-

tainly take into account what is reported in the literature. But ultimately, to effectively understand what products best meet their needs, they need to carry out their own comparisons in their own environment with their own protocols and staff.

Recommendations for Future Research

While scientifically sound, the studies reported herein were conducted on a relatively limited number of healthy subjects in a controlled laboratory setting. Although one would expect similar results in actual use settings, well-designed studies that compare the effectiveness of products containing combination CHG+IPA and PVP-I+IPA formulations in preventing catheter-related bloodstream infections over extended periods of time need to be carried out. In addition, because infection rates differ widely between different patient populations and health-care settings, it would be useful to compare the effectiveness of these combination formulations in different settings and on different populations.

Acknowledgments

I thank my colleagues who assisted in manuscript development and review: Bruce H. Wilson, Jr.; Melissa Leone, RN, BSN; Joan Lang, RN, BSN; Nancy Kramer, RN, BSN; Jim Durkin; Paul Buccetti; Debbie Benvenuto, RN, BSN, CRNI; and Todd Bailey.

ExCel_{AP} is a registered trademark of Aplicare, Inc., Meridian, CT. Chloraprep[®] and Sepp[®] are registered trademarks of Enturia, Inc., Leawood, KS. Hibiclens[®] is a registered trademark of Mölnlycke RM Ltd., Norcross, GA.

References

1. Clemence MA, Walker D, Farr BM. Central venous catheter practices: results of a survey. *Am J Infect Control*. 1995;23:5-12.
2. Maki DG, Ringer M, Alvarado CJ. Prospective randomized trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet*. 1991;338:339-343.
3. U.S. Centers for Disease Control and Prevention. Guidelines for the prevention of intravascular catheter-related infections. *MMWR*. 2002;51(No. RR-10). Accessed at <http://www.cdc.gov/mmwr/PDF/rr/rr5110.pdf> on April 5, 2007.
4. Kinirons B, Mimox O, Lafendl L, et al. Chlorhexidine versus povidone iodine in preventing colonization of continuous epidural catheters in children. *Anesthesiology*. 2001;94:239-244.
5. Meffre C, Girard R, Hajjar J, Fabry J. Is peripheral venous catheter colonisation related to antiseptic used for disinfection of the insertion site? Povidone-iodine vs. alcoholic chlorhexidine: a multicenter randomised prospective study [abstract]. *Catheter Study Group. Hygienes*. 1995;9:45.
6. Mimoz O, Mercat A, Falissard B, Richard C, Nordmann P. Chlorhexidine compared with povidone-iodine as skin preparation before blood culture. *Ann Intern Med*. 1999;131:834-837.
7. Humar A, Ostromecki A, Drenfeld J, et al. Prospective randomized trial of 10% povidone-iodine versus 0.5% tincture of chlorhexidine as cutaneous antisepsis for prevention of central venous catheter infection. *Clin Infect Dis*. 2000;31:1001-1007.

8. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Sullivan SD, Saint S. Vascular catheter site care: the clinical and economic benefits of chlorhexidine gluconate compared with povidone iodine. *Clin Infect Dis*. 2003;36:764-771.
9. Garland JS, Buck RK, Maloney P, et al. Comparison of 10% povidone-iodine and 0.5% chlorhexidine gluconate for the prevention of peripheral intravenous catheter colonization in neonates: a prospective trial. *Pediatr Infect Dis J*. 1995;14:510-516.
10. National Institute for Clinical Excellence. Infection control. Prevention of healthcare-associated infection in primary and community care. 2003. Accessed at <http://www.nice.org.uk/page.aspx?o=CG002fullguideline> on April 5, 2007.
11. Chambers, CE, Eisenhauer, MD, McNicol, LB et. al. Infection control guidelines for the cardiac catheterization laboratory: society guidelines revisited. *Catheterization and Cardiovascular Interventions* 2006. 67:78-86. Accessed at <http://www.scai.org/PDF/ID%20guidelines.pdf> on April 5, 2007.
12. Miller, DL, O'Grady, NP. Guidelines for the prevention of intravascular catheter-related infections: recommendations relevant to interventional radiology. *J Vasc Interv Radiol* 2003;14:S355-S358. Accessed at <http://www.scai.org/PDF/ID%20guidelines.pdf> on April 5, 2007.
13. Institute for Healthcare Improvement. Getting Started Kit: Prevent Central Line Infections. How-to Guide. June 14, 2006. Accessed at <http://www.ihl.org/NR/rdonlyres/0AD706AA-0E76-457B-A4B0-78C31A5172D8/0/CentralLinesHowtoGuide2006v06postedtotheweb60806.doc> on April 5, 2007.
14. Holmes SB, Brown SJ, et. al. Skeletal pin site care. National Association of orthopaedic nurses guidelines for orthopaedic nursing. *Orthopaed Nurs*. 2005;24:99-107. Accessed at <http://www.orthonurse.org/images/PDF/PinCare2005.pdf> on August 11, 2006.
15. U.S. Centers for Disease Control and Prevention. Guideline for prevention of surgical site infection 1999. *Infect Control Hosp Epidemiol* 1999;20:250-278.
16. Art GR. Combination povidone-iodine and alcohol formulations more effective, more convenient versus formulations containing either iodine or alcohol alone. *J Infus Nurs*. 2005;28:314-319.
17. Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products. Federal Register. 1994;59(116):31402-31452 (Proposed Rule). 21 CFR Parts 333 and 369. Accessed at http://www.fda.gov/cder/otcmonographs/Antimicrobial/antimicrobial_antiseptic_TF_PR_19940617.pdf on April 5, 2007.
18. United States Pharmacopeia; Washington, DC;2000. USP 27; 991.
19. United States Pharmacopeia; Washington, DC;2000. USP 27; 1532.
20. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry: skin irritation and sensitization testing of generic transdermal drug products. Rockville, MD; 1999. Accessed at <http://www.fda.gov/cder/guidance/2887fnl.htm> and <http://www.fda.gov/ohrms/dockets/98fr/990236Gd.pdf> on July 13, 2007.
21. An occlusive, chambered device specifically designed for skin patch testing [Website]. Accessed at <http://www.truetest.com/finchambers.aspx> and <http://www.hofmanenterprise.pl/english/products.php> on July 13, 2007.
22. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Medical Review of NDA 20-832. Accessed at http://www.fda.gov/cder/foi/nda/2000/20-832_CHLORAPREP%20ONE-STEP%20ANTISEPTIC_medr.pdf on April 5, 2007.
23. Enturia, Inc. Chloraprep clinical compendium. Accessed at http://www.medi-flex.com/chloraprep_com/clinical/Compendium.pdf on April 5, 2007.
24. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance. Rockville, MD: 1996. Accessed at <http://www.fda.gov/cder/guidance/959fnl.pdf> on July 5, 2007.
25. American Society of Testing and Materials. ASTM E 1173 – 01: Standard test method for evaluation of preoperative, precatheterization, or preinjection skin preparations. West Conshohocken, PA: ASTM International.
26. Williamson P, Klugman AM. A new method for the quantitative investigation of cutaneous bacteria. *J Invest Dermatol*. 1965;45:498-503.
27. Chloraprep. [Manufacturer's directions for use]. Accessed at http://www.mediflex.com/chloraprep_com/labels/3mL_Clear_label.pdf on July 5, 2007.
28. Chloraprep. [Manufacturer's directions for use]. Accessed at http://www.mediflex.com/chloraprep_com/labels/Sepp_label.pdf on July 5, 2007.
29. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Microbiology Review of NDA 20-832. Accessed at http://www.fda.gov/cder/foi/nda/2000/20-832_CHLORAPREP%20ONE-STEP%20ANTISEPTIC_microbr.pdf on April 5, 2007.
30. Infusion Nurses Society. Infusion Nursing Standards of Practice. *J Infusion Nurs*. 2006;29(1S).
31. Paulson DS. Chlorhexidine gluconate. In: Paulson DS, ed. *Handbook of topical antimicrobials. Industrial applications in consumer products and pharmaceuticals*. New York, NY: Marcel Dekker, Inc.;2003: pp. 117-122.

Received 4/5/2007 Accepted 7/20/2007

Greg Art is Director of Product Development at Aplicare, Inc. He has over twenty years experience in bringing new antiseptic products to market including those containing Alcohol, CHG, PCMX, PVP-I, and Triclosan. As an independent consultant for nearly 10 years, Greg has provided services in the areas of new product development and regulatory affairs/quality assurance for both national and international firms. His professional affiliations include membership in APIC, the American Society for Testing and Materials, the Product Development Management Association, and INS where he was a member of the editorial review board of the 2006 INS Standards of Practice.